PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

Serial No: 09/403,440

Filed: 19 January 2000

For: LANE, David.

Examiner: Davis, Minh-Tam

Art Unit: 1642

Docket No: 39749-0001APC

SECOND DECLARATION OF KAREN VOUSDEN UNDER 37 CFR' 37 C.F.R. 1.132

Assistant Commissioner for Patents
Washington, DC 20231

SIR·

I Professor Karen Vousden, hereby declare and say as follows:

1. I am the same Karen Vousden who signed the Declaration dated June 27, 2007, and filed with Applicant's submissions of July 17, 2007.

2. I am familiar with and understand the Office Action dated September 11th, 2007, and this Declaration is made in response to the Examiner's comments made in that Office Action.

3. The Examiner states that the response, including my previous Declaration, was not found persuasive. I have considered the reasons given by the Examiner in support of this conclusion and disagree with her analysis of the McCann et al paper on several points.

4. McCann et al show that 7/97 tumours have high levels of MDM2 expression (type 2, 10-50% staining) and that these are associated with low levels of p53. Table II of McCann et al only shows results for tumours that are either amplified for the *MDM2* gene (samples 10, 16 and 19 – of which only 2 show type 2 MDM2 staining) or tumours that show high MDM2 protein expression (i.e. 10-50% staining) without amplification of the gene (tumours 15, 30, 45, 47 and 60). The authors define these 7 as the MDM2+ tumours and state that these show a significant

association with low levels of p53. So tumours with high MDM2 (as defined by type 2 staining) are likely to have low p53 – this is what the authors conclude from their study.

5. The Examiner makes the statement on page 7 that *'the language "at the protein level, MDM2 tumors were significantly associated with tumors having low levels of p53 staining" (Summary, lines 7-8) indicates that not only those few breast cancers that over-express Mdm2 tend to show low levels of p53, but those that do not over-express mdm2 also show low levels of p53, supra'.*

6. Firstly, it should be pointed out that this is not an accurate quotation from the paper. In fact the paper states *"at the protein level, **MDM2**+ tumors were significantly associated....."* (emphasis added)

7. On page 983 the authors define MDM2+ as "[10-50% of tumor nuclei positive (MDM2+) Table 1]" and "MDM2+ (type 2 staining)" . This makes it absolutely clear that the authors intend the expression "MDM2+ tumors", to mean those 7 tumours with high MDM2 expression. The examiner is mistaken in interpreting this statement as indicting that "not only those few cancers that over-express Mdm2 tend to show low levels of p53, but those that do not over-express mdm2 also show low levels of p53". The authors restrict their comments to only the MDM2+ (i.e. 10-50% staining) tumours.

8. Thus, McCann et al teach that tumours with high MDM2 expression are associated with low p53 and this is only 7% of the cancers.

9. After careful consideration of the results presented in the McCann I believe it may be possible to conclude that even the tumours that express lower amounts of MDM2 (the type 1 tumours, less than 10% staining) are associated with low p53 (there are 14 of these tumours, 12 show low p53 staining and 2 show high). See, in particular Table III. The authors of McCann et al do not pay much regard to this as they limit their comments to the 7 MDM2+ tumours and one might be reluctant to draw conclusions from data that the authors have chosen not to highlight themselves.

10. If we chose to make this conclusion, then it would be true to say that MDM2 expression (either type 1 or type 2) seems to be correlated with low p53. However, this does not tell us that tumours that do not overexpress MDM2 are also associated with low p53 (as the examiner has concluded). The problem here is that we don't know what normal expression is – and it is quite possible that the type 1 expression is also represents over-expression of MDM2 compared to

normal (there is no normal tissue in the McCann et al study for comparison). The fact that most of the tumours are apparently negative for MDM2 staining (74/95) does not mean that they don't express any MDM2 – only that it is below the level of detection in this assay. For this reason it is quite hard to interpret the meaning of the less than 10% expression, which is probably why the authors have chosen to base their conclusion on the tumours that clearly over-express MDM2 – that is the type 2 staining ones.

11. On page 7 of the office action, the Examiner states *"Thus, in view that similar to those few breast cancers having over-expressed mdm2, the presence of mdm2 in most breast cancers which have no over-expression of Mdm2 is also associated with low levels of p53"* and attributes this teaching to that of McCann et al. This idea is repeated several times by the Examiner (e.g. page 8 point 2) and seems to me to form the basis of the rejection of the claims.

12. If I have understood the Examiner's arguments correctly, then I think the Examiner is basing her arguments on the fact that she believes even tumours with no over-expression of MDM2 (i.e. tumours with normal MDM2 expression, which would include most tumours) are correlated with low p53. This is not right and is a misinterpretation of the teaching of McCann et al.

13. As I said above, one does not know what overexpression of MDM2 really is, since we have no normal tissue to compare. It is most likely that both type 2 and type 1 tumours are actually over-expressing MDM2, and the tumours with negative expression are those without over-expression. These MDM2 staining-negative tumours still represent the large majority (74/95 or 78%). So, even if we take the type 1 tumours into account (which again I emphasise the authors did not, suggesting that they are not so sure about the interpretation here), the results still support our previous contention that MDM2 over-expression is not common in breast cancers. Accordingly, the McCann paper teaches that most breast cancers arise without evidence for amplification or overexpression of MDM2 and these cancers are not associated with low levels of p53 (34/74 of them have type 2 and 3 p53 staining).

14. From my reading of McCann et al, I assume that in the 40 tumours without MDM2 staining and with low levels of p53 there must be another mechanism to inactivate p53 – and that inhibiting the p53/MDM2 interaction would not necessarily work in these cases.

15. Taking McCann et al together with the study from Bottger, and without the knowledge of the invention claimed in the present application, I would conclude that a therapy based on the 12 amino acid peptide would only be expected to be effective in 7% (or at the most 22%) of breast

cancers (i.e. those with over-expressed MDM2) and would suggest that most breast cancers would not benefit from such therapy.

16 Despite the comments made by the Examiner in response to my previous Declaration and for the reasons provide above, I maintain by belief that at the time of the McCann et al paper it would have been reasonable to assume that in cells where low or normal levels of MDM2 exist, inactivation of the p53 pathway to allow aberrant tumour growth would have arisen from another mechanism.

17. For the reasons set forth in paragraphs 4 through 17 of this Declaration, I believe the results disclosed in US09/403,440 where they have shown that inhibition of MDM2:p53 has a growth reducing effect in tumour cells in which MDM2 is not over-expressed and consequently is a useful therapy for these cells was surprising given the understanding of the mechanisms involved in p53 function at the time US09/403,440 was filed.

18. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Signed _____ on 6TH MARCH 2008